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DLA PIPER US LLP
4365 EXECUTIVE DRIVE
SUITE 1100
SAN DIEGO, CA 92121-2133

EXAMINER	
NEGIN, RUSSELL SCOTT	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/087,441	PALSSON ET AL.	
	Examiner	Art Unit	
	RUSSELL S. NEGIN	1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 March 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-16 and 18-74* is/are pending in the application.

4a) Of the above claim(s) *66-69* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-16,18-65 and 70-74* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Comments

Applicants' amendments and request for reconsideration in the communication filed on 17 March 2008 are acknowledged and the amendments are entered.

Claims 1-16, and 18-74 are pending and claims 1-16, 18-65, and 70-74 are examined in this Office action.

Claims 66-69 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected Group, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 7 June 2004.

Withdrawn Rejections

The rejections of claims 1-16 and 18-33 under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter are withdrawn in view of amendments to the instant set of claims filed on 17 March 2008.

The rejection of claim 18 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is withdrawn in view of amendments to the instant claim filed on 17 March 2008.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

The following rejection is reiterated from the previous Office action:

35 U.S.C. 103 Rejection #1:

Claims 1-9, 11, 14-15, 18-28, 30, 32-33, 34-42, 44-45, 48-49, 51-60, 62-63, and 70-74 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hatzimanikatis et al. [AIChE Journal, 1996, volume 42, pages 1277-1292].

Claim 1 is drawn to a computer readable medium or media having stored thereon instructions to perform the following steps:

--providing a data structure relating a plurality of reactants to a plurality of reactions of a biochemical reaction network, wherein each of said reactions comprises a reactant identified as a substrate of the reaction, a reactant identified as the product of the reaction and a stoichiometric coefficient relating said substrate and said product, and wherein at least one of said reactions is a regulated reaction;

--providing a constraint set for said plurality of reactions, wherein said constraint set comprises a variable constraint for said regulated reaction

--determining at least one flux distribution that minimizes or maximizes an objective function when said constraint set is applied to said data structure, wherein said at least one flux distribution determines a systemic property of said biochemical reaction network, and wherein said systemic property is dependent upon the flux through said regulated reaction, and

--providing information resulting from the method to a user.

Claim 34 is drawn to a method for determine a systemic property of a biochemical reaction network, comprising:

--providing a data structure relating a plurality of reactants to a plurality of reactions of a biochemical reaction network, wherein each of said reactions comprises a reactant identified as a substrate of the reaction, a reactant identified as a product of the reaction and a stoichiometric coefficient relating said substrate and said product, and wherein at least on of said reactions is a regulated reaction;

--providing a constraint set for said plurality of reactions, wherein said constraint set comprises a variable constraint for said regulated reaction;

--providing a condition-dependent value to said variable constraint;

--providing an objective function;

--determining at least one flux distribution that minimized or maximizes said objective function when said constraint is applied to said data structure, wherein said at least one flux distribution is determinative of a systemic property of said biochemical reaction network; and

--providing said systemic property of said biochemical reaction network to a user.

Claim 71 is drawn to a method for determining a systemic property of a biochemical reaction network at a first and a second time comprising:

--providing a data structure relating a plurality of reactant to a plurality of reactions of a biochemical reaction network wherein each of said reactions comprises a reactant identified as a substrate of the reaction, a reactant identified as a product of the reaction and a stoichiometric coefficient relating said substrate and said product, and wherein at least one of said reactions is a regulated reaction;

--providing a constraint for said plurality of reactions, wherein said constraint set comprised a variable constraint for said regulated reaction;

--providing a condition-dependent value to said variable constraint;

--providing an objective function;

--determining at least one flux distribution at a first time that minimizes or maximizes said objective function when said constraint set is applied to said data structure, thereby determining a systemic property of said biochemical reaction network at said first time;

--modifying said value to said variable constraint;

--repeating step (e) wherein said at least one flux distribution is determined at a second time, thereby determining a systemic property of said biochemical reaction network at a second time; and

--providing said systemic property of said biochemical reaction network to a user at said first, second, or first and second time.

These three independent claims have the same three core concepts: 1. providing of a data structure containing a system of reactions where a subset of the reactions is regulated, 2. providing a constraint set under which the reactions are operated (of which a subset of the constraints are variable constraints), 3. optimizing an objective function in order to determine a systemic property resulting from the system as a result of a flux distribution analysis. The results are provided to a user.

Claim 34 has the extra limitation of a condition dependent constraint.

Claim 71 has the extra limitation of a condition dependent constraint and the further limitation of iteratively modifying the variable constraint.

The article of Hatzimanikatis et al. studies analysis and design of metabolic reaction networks via mixed integer linear optimization.

The first several sentences of the abstract of Hatzimanikatis et al. state:

> Improvements in bioprocess performance can be achieved by genetic modifications of metabolic control structures. A novel optimization problem helps quantitative understanding and rational metabolic engineering of metabolic reaction pathways.

Hatzimanikatis et al. continues in the abstract to describe that the problem to be solved is finding the optimal regulatory structure for maximization of phenylalanine selectivity in the microbial aromatic synthesis pathway.

An illustration of the reaction pathway studies on Hatzimanikatis et al. is shown in Figure 1 on page 1283 where several of the reactions are regulated (i.e. dotted lines in the Figure indicate regulatory reactions).

The system is mathematically described on page 1279 in Equation 1 and the paragraph bridging the first and second columns, which states:

> Consider a metabolic system consisting of n metabolites and m enzymatically-catalyzed reactions. We are in [sic] interested in studying how modifications of the expression levels and of the properties of the enzymes that catalyze these reactions affect metabolic functions of the system, such as metabolite concentrations, fluxes, and specific growth rate.

Consequently, flux distributions through this amino acid synthesis pathway are studied.

Constraints are described on pages 1282-1283 of Hatzimanikatis et al. The constraints include mass balances (non variable constraints), constraints based on continuous variables (variable constraints), and logical constraints based on the presence of certain regulatory loops (binary variable constraints). Some of the constraints (i.e. the binary constraints) are condition dependent on the presence of certain regulated reactions in the network.

The values of the constraints are conditionally dependent on which of the eight pathways of solutions in Figure 2 on page 1284 of Hatzimanikatis et al. is selected.

The objective function is listed in Equation 12 on page 1281 of Hatzimanikatis et al. The goal of the study of Hatzimanikatis et al. is to maximize and minimize this function.

Table 1 on page 1285 of Hatzimanikatis et al. shows the solution for the continuous variables for six iterations in which variable functions and constraints are modified (i.e. optimized). Table 1 is also provides the results of the calculation to a user.

Claims 2 and 35 are further limiting in that said variable constraint is dependent upon the outcome of at least one reaction.

Claims 3 and 36 are further limiting in that said variable constraint is dependent upon the outcome of at least one regulatory event.

Claims 4 and 27 are further limiting in that the variable constraint is dependent on time.

Claims 5 and 38 are further limiting wherein said variable constraint is dependent upon the presence of a biochemical network participant.

Figure 2 on page 1284 of Hatzimanikatis et al. illustrates the eight best solution pathways for solving the optimization problem. Each of these solutions is interpreted to be calculated at a different time. Each pathway has a different set of reactions and regulatory events based on the calculation of different logical constraints (binary

variable constraint that indicate the existence or nonexistence of various regulatory loops- see bottom of second column of page 1282).

Claims 6 and 39 are further limiting wherein the participant is a substrate or product.

The reactions in Figure 1 of Hatzimanikatis et al. list substrates and products.

Claims 7 and 40 are further limiting wherein the said biochemical reaction network comprises metabolic reactions.

The pathway described in Figure 1 of Hatzimanikatis et al. is a metabolic pathway.

Claims 8 and 41 are further limiting comprising a regulatory data structure, wherein said variable constraint is dependent upon an outcome of a regulatory event represented by a data structure.

Logical constraints are binary variable constraints that indicate the existence or nonexistence of various regulatory loops- see bottom of second column of page 1282 of Hatzimanikatis et al.

Claims 9 and 42 are further limiting wherein one of the regulatory events can be inhibition or activation of a protein.

Hatzimanikatis et al. teaches activation and inhibition of in metabolism in the third paragraph from the bottom in column 2 on page 1280 as examples of regulation events that affect the studied metabolic network.

Claims 11 and 44 are further limiting wherein said biochemical network and said regulatory data structure represent reactions or events that occur in a single cell.

The last line of page 1277 of Hatzimanikatis et al. indicates that the pathway occurs in a cell.

Claims 14 and 48 are further limiting wherein there is a constraint function that correlates an outcome of a variable event with a variable constraint.

These functions are given on page 1283 of Hatzimanikatis et al. in Equations 22-26.

Claims 15 and 49 are further limiting wherein the constraint is binary.

The logical constraints of Hatzimanikatis et al. are binary constraints indicating the presence or absence of certain regulatory events in the synthesis pathway.

Claim 18 is further limiting comprising a range of feasible flux distributions.

Claims 19 and 53 are further limiting wherein the commands comprise an optimization problem. Claim 20 and 54 are further limiting wherein the optimization is linear or nonlinear optimization.

The objective of the study of Hatzimanikatis et al. is to use mixed-integer linear optimization to analyze a metabolic reaction (i.e. title). In doing so, flux distributions are calculated between reactions (i.e. see equation 1 on page 1279).

Claim 21 is further limiting that there is a user interface capable of sending at least one command for modifying said data structure. Claim 22 is further limiting wherein said user interface further comprises links which a user may select to access additional information relating to said plurality of reactions.

Figure 2 on page 1284 of Hatzimanikatis et al. illustrates such a user interface with visual links to each of the eight regulatory pathways. Each of the eight pathways is based on different optimization constraints resulting in different reaction networks.

Claims 23 and 56 are further limiting wherein said data structure comprises a set of linear algebraic equations.

Claims 24 and 57 are further limiting wherein said data comprises a matrix.

The equations of Hatzimanikatis et al. (i.e. equations 6-7 on page 1280 of Hatzimanikatis et al.) are examples of linear algebraic equations with relevant matrices.

Claims 25 and 58 are further limiting by demonstrating flux distributions as a flux distribution map.

Claim 26 is further limiting by annotating reactants and products.

Claim 27 is further limiting wherein a reactant is assigned a compartment.

Claim 28 is further limiting wherein a reactant is assigned to a compartment and another reactant is assigned to a different compartment.

Figure 1 of Hatzimanikatis et al. lists a flux distribution map with each member of the network being annotated with an abbreviation. Each member of the pathway is assigned to a different compartment within the Figure of Hatzimanikatis et al.

Claim 32 and 59 are further limiting wherein a specific listing of biochemical processes lists biosynthesis of an amino acid as a possible result of the network of reactions.

The objective of the pathways of Hatzimanikatis et al. is biosynthesis of the amino acid phenylalanine (see abstract).

Claims 33 and 62 are further limiting wherein there are a plurality of regulated reactions and variable constraints.

Figures 1-3 of Hatzimanikatis et al. illustrate a plurality of regulated reactions governed by a plurality of variable constraints.

Claim 45 is further limiting wherein the regulatory event comprises a regulatory reaction.

The regulatory events in Hatzimanikatis et al. are the regulatory reactions described in Hatzimanikatis et al. (i.e. Figure 1 of Hatzimanikatis et al.)

Claim 51 is further limiting wherein said constraint function correlates a first set of outcomes of said regulatory data structure with a first binary value and a second set of outcomes of said regulatory data structure with a second binary value.

Claim 52 is further limiting wherein said constraint function correlates a set of outcomes of said regulatory data structure with a single integer value.

The logical constraints in the bottom of the second column of page 1282 are binary variables indicating the presence of certain outcomes (i.e. presence) of certain regulatory reactions. Binary variables have single integer values.

Claim 55 is further limiting comprising a step of modifying said data structure or said constraint set, or both. Claim 63 is further limiting wherein the constraint function is binary.

Figure 2 of Hatzimanikatis et al. illustrates eight modifications of the data structure. The presence of a regulatory reaction is based on the result of a binary constraint function indicating its existence.

Claim 60 is further limiting wherein a systemic property is chosen from a given list including production of an amino acid.

The objective of the pathways of Hatzimanikatis et al. is biosynthesis of the amino acid phenylalanine (see abstract).

Claim 70 is further limiting wherein a plurality of said reactions are regulated reactions and said constraints for said regulated reactions comprise boundary values.

Claim 72 is further limiting wherein said value is modified based on said flux distribution at said first time.

Claim 73 is further limiting wherein said value is modified based on a change in an environmental condition.

Claim 74 is further limiting wherein steps of claim 71 for a specified number of time points.

Equations 14 and 15 on page 1282 of Hatzimanikatis et al. illustrates boundary constraints intended to limit the pathway to physiological conditions. The pathways are consequently modified in such a way to function under physiological conditions. The multiple iterations in Table 1 of Hatzimanikatis et al. are interpreted to be conducted at multiple time points.

Hatzimanikatis et al. fail to teach the automated aspect of the instant claims.

In *KSR Int 'l v. Teleflex*, the Supreme Court, in rejecting the rigid application of the teaching, suggestion, and motivation test by the Federal Circuit, indicated that

> The principles underlying [earlier] cases are instructive when the question is whether a patent claiming the combination of elements of prior art is obvious. When a work is available in one field of endeavor, design incentives and other market forces can prompt variations of it, either in the same field or a different one. If a person of ordinary skill can implement a predictable variation, § 103 likely bars its patentability.

KSR Int'l v. Teleflex Inc., 127 S. Ct. 1727, 1740 (2007).

Applying the KSR standard of obviousness to the automate and computerize the method of Hatzimanikatis et al., the Examiner concludes that such addition is a use of

known technique to improve similar methods or devices. Using the known technique of automating the process on a computer to provide reliable and expedient results would have been obvious to one of ordinary skill.

Response to Arguments:

Applicant's arguments filed 17 March 2008 have been fully considered but they are not persuasive.

Applicant has two arguments regarding this obviousness prior art rejection.

The first argument is that the intended invention and the prior art do not coincide with solving the same intended problem. Applicant states that the instant invention is not drawn to determining and optimizing the "regulatory superstructure" of a set of reactions governing a process, but rather, it is drawn to optimizing a set of optimal values of networks. Applicant states this succinctly on page 17 of the Remarks, wherein applicant states:

> Contrary to Hatzimanikatis, the claimed methods are not directed to finding a regulatory structure to optimize the objective, but rather at imposing information about regulation in determining optimal values of networkd with one or more regulatory constraints defined.

This argument, while fundamental, is not persuasive because while applicant makes it clear in the Remarks as to what is the intention of the claimed invention, the instant set of claims still read on the concepts in Hatzimanikatis et al. In other words, applicant has not made it clear as to how the intended invention cause the claims and corresponding definitions of relevant terminology in the specification to not be made obvious by the document of Hatzimanikatis et al.

The second argument of applicant is that Hatzimanikatis et al. does not provide the computerized aspect of the instant set of claims. This is not found to be persuasive in view of the rational for automation recited in the rejection above.

The following rejection is reiterated from the previous Office action:

35 U.S.C. 103 Rejection #2:

Claims 10, 12, 43, and 46 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hatzimanikatis as applied to claims 1-9, 11, 14-15, 18-28, 30, 32-33, 34-42, 44-45, 48-49, 51-60, 62-63, and 70-74 above, and further in view of Grewal et al. [Protein Engineering, volume 7, 1994, pages 205-211].

Claims 10 and 43 are further limiting wherein the regulatory event is due to a signal transduction pathway.

Claims 12 and 46 are further limiting wherein said biochemical reaction network represents reactions that occur in a first cell in a population of cells and said regulatory data structure events occur in a second cell.

Hatzimanikatis et al. makes obvious the method of using linear optimization to optimize a regulated reaction, as set forth above.

Hatzimanikatis et al. does not teach the method of signal transduction in cell populations or multicellular organisms.

The article of Grewal et al., entitled, "Computer modeling of the interaction between human choriogonadotropin and its receptor," states in its introduction:

> The endocrine action of the ovarian luteinizing hormone (LH) and the placental choriogonadotropin (CG), is mediated by the LF/CG receptor. Binding of LH or CG to the receptor on gonadal target cells results in the increase in adenyl cyclase activity… which is

> mediated by membrane-associated intracellular G-proteins… Increase in cAMP concentration finally leads to steroid synthesis and secretion…, thus regulating gonadal functions. Hormonal recognition by the LH/CG receptor involves a site of interaction in the extracellular domain of the receptor…

Consequently, Grewal et al. describe a reaction pathway in a multicellular organism where the reaction in one cell mediates cellular interactions in the multicellular organism (i.e. signal transduction pathways).

Grewal et al. state in the final sentence of the introduction on page 205 and the final sentence of the discussion on page 211, respectively:

> This [study of interactions] has led to the identification of sequence regions defining the hormone binding site of the LH/CG receptor and the 3-D modeling of the interaction between the hormone and the receptor….
> Three-dimensional mapping of the regions involved in the hCG—receptor recognition has important implications. It can lead to the design of specific peptide antagonists for therapeutic applications as well as for exploring the mechanism of hormone action subsequence to receptor binding.

It would have been obvious to modify Hatzimanikatis et al. by incorporating the signal transduction method of Grewal et al. where the motivation would have been to better design peptide antagonists for therapeutic applications such as through the better understanding of hCG-receptor interaction by three dimensional mapping, as taught by Grewal et al on page 211.

Response to Arguments:

Applicant's arguments filed 17 March 2008 have been fully considered but they are not persuasive. Applicant alleges that since Hatzimanikatis et al. is deficient, this rejection is also deficient. As discussed above, since Hatzimanikatis et al. is not deficient, this obviousness prior art rejection is not deficient.

The following rejection is reiterated from the previous Office action:

35 U.S.C. 103 Rejection #3:

Claims 31 and 64-65 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hatzimanikatis et al. as applied to claims 1-9, 11, 14-15, 18-28, 30, 32-33, 34-42, 44-45, 48-49, 51-60, 62-63, and 70-74 above, and further in view of Liao et al. [Biotechnology and Bioengineering, volume 52, 1996, pages 129-140].

Claims 31 and 64 are further limiting wherein a gene database relating one or more reactions in said data structure with one or more open reading frames or proteins in a particular organism.

Claim 65 is further limiting comprising identifying an open reading frame that encodes a protein that performs a plurality of reactions.

Hatzimanikatis et al. makes obvious a method of using linear optimization to optimize a regulated reaction, as set forth above.

Hatzimanikatis et al. does not teach use of open reading frames and gene databases.

The article of Liao et al. investigates pathway analysis, engineering, and physiological considerations for redirecting central metabolism.

Figure 3 on page 132 of Liao et al. illustrates a data base of relevant expression from different mutant genes with open reading frames expressing the necessary

proteins listed perform the metabolic pathways of Liao et al. in order to produce glucose.

The sentences bridging columns 1 and 2 on page 137 of Liao et al. state:

> We have presented evidence suggesting that some of these metabolites serve as an internal signal in regulating glucose transport, heat shock response, and nitrogen regulation.

Consequently, the metabolites associated with the genes play a significant role in regulating biologically important responses.

It would have been obvious to someone of ordinary skill in the art at the time of the instant invention to modify Hatzimanikatis et al., by incorporating the genetic analyses of the metabolic pathways of glucose as taught by Liao et al. where the motivation would have been a better understanding of an internal method of regulating biological responses such as glucose transport, heat shock response, and nitrogen regulation as taught by Liao et al. on page 137.

Response to Arguments:

Applicant's arguments filed 17 March 2008 have been fully considered but they are not persuasive. Applicant alleges that since Hatzimanikatis et al. is deficient, this rejection is also deficient. As discussed above, since Hatzimanikatis et al. is not deficient, this obviousness prior art rejection is not deficient.

The following rejection is reiterated from the previous Office action:

35 U.S.C. 103 Rejection #4:

Claims 16 and 50 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hatzimanikatis et al. as applied to claims 1-9, 11, 14-15, 18-28, 30, 32-33, 34-42, 44-45, 48-49, 51-60, 62-63, and 70-74 above, and further in view of Kim et al. [US 2002/00087275 A1; filed 31 July 2001].

Claims 16 and 50 are further limiting by incorporating Boolean operators into the reaction pathway.

Hatzimanikatis et al. makes obvious a method of using linear optimization to optimize a regulated reaction, as set forth above.

Hatzimanikatis et al. does not teach usage of Boolean analysis in the reaction pathways.

The study of Kim et al. studies visualization and manipulation of biomolecular relationships using graph operators. Figure 1 of Kim et al. illustrates such a graph theory. Specifically, Paragraph [0097] describes use of Boolean variables when examining the reaction network.

This analysis of Kim et al. allows for computational algorithms for representing and analyzing large and heterogeneous molecular biological data (see paragraph [0002]). The last sentences of paragraph [0010] of Kim et al. explain a disadvantage of the prior art improved upon in Kim et al.:

> However the computation of these [prior art] systems were carried out at the database level by querying a database for all potential consecutive binary gene pairs, and subsequently, integrating them into pathways…. More complex analyses such as comparing disparate data sets, exploring gene network structures, and inferring pathways and gene functions, are either beyond the capacity of these systems or computationally too expensive to perform.

It would have been obvious to someone of ordinary skill in the art at the time of the instant invention to modify Hatzimanikatis et al., by incorporating the genetic

graphing algorithms taught by Kim et al. where the motivation would have been a better understanding of complex metabolic networks, as described in paragraphs [0002] and [0010] of Kim et al.

Response to Arguments:

Applicant's arguments filed 17 March 2008 have been fully considered but they are not persuasive. Applicant alleges that since Hatzimanikatis et al. is deficient, this rejection is also deficient. As discussed above, since Hatzimanikatis et al. is not deficient, this obviousness prior art rejection is not deficient.

The following rejection is reiterated from the previous Office action:

35 U.S.C. 103 Rejection #5:

Claims 13 and 47 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hatzimanikatis et al. as applied to claims 1-9, 11, 14-15, 18-28, 30, 32-33, 34-42, 44-45, 48-49, 51-60, 62-63, and 70-74 above, and further in view of Vissing et al. [Neurology, 1996, volume 47, pages 766-771].

Claims 13 and 47 are further limiting in that the events occur in a multicellular organism.

Hatzimanikatis et al. makes obvious a method of using linear optimization to optimize a regulated reaction, as set forth above.

Hatzimanikatis et al. does not teach regulated reaction networks in multicellular organisms.

The study of Vissing et al. examines the sources of enhanced glucose production during exercise in humans with blocked glycolysis caused by muscle phosphofructokinase deficiency.

The purpose of understanding this phenomenon is relevant for better understanding of diseases involving altered glucose production during glycolysis (i.e. McArdle's disease in the paragraph bridging columns 1 and 2 on page 766).

It would have been obvious to someone of ordinary skill in the art at the time of the instant invention to modify Hatzimanikatis et al., by incorporating the metabolic pathway of glycolysis in humans of Vissing et al. where the motivation would have been a better understanding of diseases affected by abnormal glycolysis, as taught on page 766 of Vissing et al.

Response to Arguments:

Applicant's arguments filed 17 March 2008 have been fully considered but they are not persuasive. Applicant alleges that since Hatzimanikatis et al. is deficient, this rejection is also deficient. As discussed above, since Hatzimanikatis et al. is not deficient, this obviousness prior art rejection is not deficient.

Conclusion

No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Papers related to this application may be submitted to Technical Center 1600 by facsimile transmission. Papers should be faxed to Technical Center 1600 via the central PTO Fax Center. The faxing of such pages must conform with the notices published in the Official Gazette, 1096 OG 30 (November 15, 1988), 1156 OG 61 (November 16, 1993), and 1157 OG 94 (December 28, 1993)(See 37 CFR § 1.6(d)). The Central PTO Fax Center Number is (571) 273-8300.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Russell Negin, Ph.D., whose telephone number is (571) 272-1083. The examiner can normally be reached on Monday-Friday from 7am to 4pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's Supervisor, Marjorie Moran, Supervisory Patent Examiner, can be reached at (571) 272-0720.

Information regarding the status of the application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information on the PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/RSN/
Russell S. Negin
13 July 2008

/Michael Borin, Ph.D./
Primary Examiner, Art Unit 1631